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Behavioral and Social Phenotypes in Boys With 47,XYY Syndrome or 47,XXY Klinefelter Syndrome

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KEY WORDS
XXY, XYY, Klinefelter syndrome, autism, ADHD

ABBREVIATIONS
ADHD—attention-deficit/hyperactivity disorder
ASD—autism spectrum disorder
CBCL—The Child Behavior Checklist
CPRS-R—Conners' Parent Rating Scale–Revised
DSM-IV—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
KS—47,XXY Klinefelter syndrome
SCQ—Social Communication Questionnaire
SES—socioeconomic status
XYY—47,XYY syndrome

Dr Tartaglia is an expert witness regarding behavior in Klinefelter syndrome. She also serves as the Medical Director of The XXYY Project (a volunteer position).

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abstract

OBJECTIVE: To contrast the behavioral and social phenotypes including a screen for autistic behaviors in boys with 47,XYY syndrome (XYY) or 47,XXY Klinefelter syndrome (KS) and controls and investigate the effect of prenatal diagnosis on the phenotype.

METHODS: Patients included 26 boys with 47,XYY, 82 boys with KS, and 50 control boys (ages 4–15 years). Participants and parents completed a physical examination, behavioral questionnaires, and intellectual assessments.

RESULTS: Most boys with XYY or KS had Child Behavior Checklist parental ratings within the normal range. On the Child Behavior Checklist, mean problem behaviors *t* scores were higher in the XYY versus KS groups for the Problem Behavior, Externalizing, Withdrawn, Thought Problems, and Attention Problems subscales. On the Conners' Parent Rating Scale–Revised, the XYY versus KS group had increased frequency of hyperactive/impulsive symptoms ($P < .006$). In addition, 50% and 12% of the XYY and KS groups, respectively, had scores >15 for autism screening from the Social Communication Questionnaire. For the boys with KS, prenatal diagnosis was associated with fewer problem behaviors.

CONCLUSIONS: A subset of the XYY and KS groups had behavioral difficulties that were more severe in the XYY group. These findings could guide clinical practice and inform patients and parents. Boys diagnosed with XYY or KS should receive a comprehensive psychoeducational evaluation and be screened for learning disabilities, attention-deficit/hyperactivity disorder, and autism spectrum disorders. *Pediatrics* 2012;129:769–778

Two sex chromosome aneuploidy disorders affecting male individuals, 47, XYY syndrome (XYY) and 47,XXY Klinefelter syndrome (KS), are relatively common and underdiagnosed, and their distinguishing features are not well known. XYY syndrome occurs in 1 of 1000 male individuals and KS, the most common human sex chromosome disorder,[1–3] occurs in 1 of 426 to 1 of 1000 male individuals.[4] Some physical, cognitive, and behavioral characteristics of boys with XYY resemble those observed in KS, including tall stature, verbal learning disabilities, and attentional deficits[1–8]; however, boys with XYY have normal pubertal development and testosterone levels, whereas boys with KS experience childhood-onset testicular failure.[5,8–14]

The cognitive phenotypes are similar in XYY and KS, including language-based learning disabilities and mild deficits in general cognitive ability as measured by full-scale IQ, academic achievement, verbal memory, and attention.[15–20] Delayed speech development requiring speech therapy[6,11,18,19,21,22] has also been observed in both boys with XYY and boys with KS. Thus, there appears to be considerable overlap in the cognitive phenotypes in these 2 disorders,[15] but the similarities and differences of the behavioral phenotypes are not as well known. Behavioral features described in XYY include increased risk of impulsivity[5,23,24] and difficulties related to behavioral dysregulation.[16,17,24–31] In addition, boys with XYY have an increased risk for features consistent with autism spectrum disorders (ASD),[11,32–34] which has also been described to a lesser extent in KS.[34,35] In contrast, the behavioral phenotype of KS includes an increased tendency toward shyness, diminished self-esteem,[36,37] anxiety, and social isolation.[29,38,39]

Most behavioral research on these syndromes was conducted 10 to 20 years ago, with varied ascertainment (population-based versus clinic-based), small sample sizes, and wide age ranges (children versus adults).[5,16–18,25,29,30,40] The goal of this study was to compare and contrast the behavioral and social phenotypes (including a screen for autistic behaviors) in boys with XYY, boys with KS, and age-matched control boys, and to investigate the effect of prenatal versus postnatal ascertainment on the observed behavioral phenotypes.

METHODS

Participants

Participants were recruited for research participation from the pediatric endocrinology clinic at Thomas Jefferson University, Internet postings, or self-referral. The study was approved by the Human Studies Committee at Thomas Jefferson University and University of Texas Southwestern Medical School. All participants and their parents gave informed consent and assent (age-appropriate). The clinical evaluation was performed at Thomas Jefferson University, and confirmatory karyotyping was performed by the clinical cytogenetics laboratory at University of Texas Southwestern Medical School.

Assessment Procedures

Participants and parents completed a physical examination, behavioral questionnaires, and intellectual assessments during a 2-day testing session. Parents were asked about previous diagnoses of attention and autism disorders. The results of cognitive testing were reported previously.[15]

Anthropometric Measurements

The clinical assessment included measurement of height, weight, and head circumference that were converted to SD scores by using age- and gender-specific norms.[41,42] Pubertal development was assessed by an experienced pediatric endocrinologist (J.L.R.) and included evaluation of testicular volume (Prader orchidometer[43]) and pubic hair development (Tanner method[44]).

Cognitive Evaluation

Participants were individually administered the Differential Ability Scales.[45] General Conceptual Ability is a general index score.

Socioeconomic Status

Socioeconomic status (SES) estimate was calculated for children by using the Hollingshead 2-Factor Index of Social Status based on education and occupation of parents.[46] Higher SES is associated with higher levels of parental education.

Behavioral Questionnaires

The primary caregiving parent of each child completed the parent questionnaires and the child completed the child questionnaires under the supervision of the examiner. (See Supplemental Information for additional detail)

Parent Questionnaires

1. The Child Behavior Checklist (CBCL)[47] is a standardized measure of behavior problems and social competency in children ages 2 to 18 years and includes *t* scores for 10 problem behavior areas and 3 social competency areas (activities, social, and school). The behavior problems scales include internalizing, externalizing, and total behavior domain scores.
2. Conners' Parent Rating Scale–Revised-Long Version (CPRS-R)[48] is a standardized measure assessing parental report of attention problems, hyperactivity, impulsivity, and other behavioral symptoms associated with attention-deficit/hyperactivity disorder (ADHD) in children ages 3 to 17 years. Subscales include Oppositional, Cognitive Problems/Inattention, Hyperactivity,

Anxious-Shy, Perfectionism, Social Problems, and Psychosomatic. Index scales include Restless-Impulsive Global index, Emotional Lability Global index, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV): Inattentive index, and DSM-IV: Hyperactive-Impulsive index.

3. The Social Communication Questionnaire (SCQ)[49] is a screen for autistic behaviors and includes 40 items that were determined to be the most predictive for autism diagnoses from the Autism Diagnostic Interview. The Current version is used for children 4 to 5 years of age, and the Lifetime version is for children 6 years and older.

Child Self-Report Questionnaires

1. The Children's Depression Inventory[50] is a self-report measure for assessment of depression in children ages 6 to 17.
2. The Revised Child's Manifest Anxiety Scale[51] measures self-reported anxiety symptoms in children ages 6 to 19.

Genetic Testing

A peripheral blood karyotype was obtained for all XYY and KS participants. Controls were not karyotyped but are presumed to have a normal karyotype (46,XY), as the prevalence of chromosome abnormalities in unselected male individuals is <1%.[52]

Statistics

Raw scores were converted to *t* scores (mean of 50, SD of 10), based on the test-specific norms. Results are presented as the mean ± SD. We used analysis of variance to test for statistically significant differences between the XYY, KS, and control groups. We also performed post hoc analysis of covariance for the XYY and KS groups separately, comparing behavioral features in those diagnosed in utero versus those diagnosed after birth. Pearson correlations were performed for continuous variables and Fisher's exact test was performed for the comparison of dichotomous variables. All *P* values are provided without adjustment for multiple comparisons, and *P* values ≤.05 were considered statistically significant.

RESULTS

Genetic Results

Karyotype results showed 26 boys with XYY and 82 boys with 47,XXY; no mosaicism was detected.

Demographics and Auxologic Results

Our study included 26 boys with XYY, 82 boys with KS, and 50 control boys, ages 4 to 15 years (Table 1). The 3 groups had similar age, SES, race, and pubic hair Tanner stage development (Table 1) and came from a broad US geographic distribution. Most participants were white. The boys with XYY or XXY were, on average, taller than the control boys ($P <$ .0001), but had similar weight SD score. Overall, testicular volume SD score was the lowest in the boys with KS ($P <$ .0001), consistent with testicular failure in this group. Testicular volume was increased in the boys with XYY, compared with controls (>1 SD in 13/25 boys with XYY [ages 4.3–13.6 years]), perhaps reflecting early pubertal development. Most of these 13 boys with testicular enlargement had Tanner 1 pubic hair development. Testicular volume SD scores were significantly related to height SD scores ($r = 0.48$, $P = .01$) but not head circumference SD scores. Head circumference differed in the 3 groups ($P <$ .03) and was highest in the boys with XYY (Table 1).

Diagnosis of XYY was made prenatally in 6 of 26 boys (routine prenatal screening), in infancy in 4 (2 for hypotonia, 1 for genitalia, and 1 for other), in childhood (ages 2–12 years) in 15 (2 for language issues, 3 for behavior issues, and 10 for other developmental reasons), and after age 12 in 1 (behavior issues). Of the 26 boys with XYY, 12 (46%) received special education services in school, 24 (92%) had received speech and/or reading therapy, and 20 (77%) received occupational and/or physical therapy. No boys with XYY were diagnosed with testicular failure or had received previous testosterone treatment.

Diagnosis of KS was made prenatally in 44 of 82 boys (routine prenatal screening), in infancy in 6 (1 for hypotonia, and 5 for other developmental reasons), in childhood (ages 2–12 years) in 28 (8 for language issues, 6

TABLE 1 Demographics and Auxologic Measurements (Mean ± SD)

	XXY	XYY	Controls	*P* value[a]
n	82	26	50	
Age	9.2 ± 2.5	9.5 ± 2.8	9.5 ± 2.9	.87
SES	50 ± 11[b]	52 ± 10	54 ± 9	.05
Height SDS	0.8 ± 1.1	1.0 ± 1.2	0.1 ± 0.9	.0001[a]
Weight SDS	0.6 ± 1.2	0.7 ± 1.2	0.5 ± 1.1	.57
Head circumference SDS	0.3 ± 1.5[b]	1.2 ± 2.1[c]	0.9 ± 1.4	.03
Tanner stage-pubic hair	1.4 ± 0.8	1.4 ± 1.1	1.3 ± 0.8	.91
Testicular volume SDS (mean of 2)	−1.0 ± 1.6[b]	2.8 ± 4.1[c]	1.1 ± 2.5	.0001[a]
Race (% Caucasian)	81%	88%	78%	.53
General conceptual ability standard score	88 ± 14[b]	91 ± 17[d]	110 ± 16	< .0001[a]

[a] ANOVA, comparison of 3 groups.
[b] $P <$ .05, XXY versus controls, ANOVA (post hoc).
[c] $P <$ .05, XYY versus XXY, ANOVA (post hoc).
[d] $P <$ .05, XYY versus controls, ANOVA (post hoc).

for behavior issues, 1 for tall stature, and 13 for other developmental reasons), and after age 12 in 4 (1 for language issues and 3 for puberty issues). Of the 82 boys with KS, 16 (20%) had received special education services in school, 60 (73%) received speech and/or reading therapy, and 49 (59%) received occupational and/or physical therapy. No boys with KS had received testosterone treatment before or at the time of the evaluation.

The control boys had heights and weights between the 5th and the 95th percentiles. None had a prior diagnosis of learning disability or ADHD.

Cognitive Results

Results from the Differential Abilities Scale revealed, on average, higher General Conceptual Ability *t* scores in the control group, compared with the XYY and KS groups (Table 1, $P < .0001$). Performance in the XYY and KS groups was similar and was published previously.[15]

Parent Behavioral Questionnaire Results

1. CBCL: Behavioral Problems and Social Competence:

In general, most of the boys with XYY or KS had scores within 2 SDs of the population mean across all Behavioral and Social Competence domains (Fig 1A). When behaviors were compared for the 3 groups, the higher scores in a subset of boys with XYY and KS led to significant differences, compared with the control group, on all CBCL scales (Table 2). The mean *t* scores for the XYY group were significantly higher compared with the KS group for Externalizing Total, Withdrawn, Thought Problems, Attention Problems, and Aggressive Behavior ($P < .05$).

Prenatal diagnosis was not a significant covariate for the boys with XYY. For the boys with KS, diagnosis in utero was associated with fewer problem behaviors on the Somatic ($P < .003$) and Thought Problems subscales ($P < .02$).

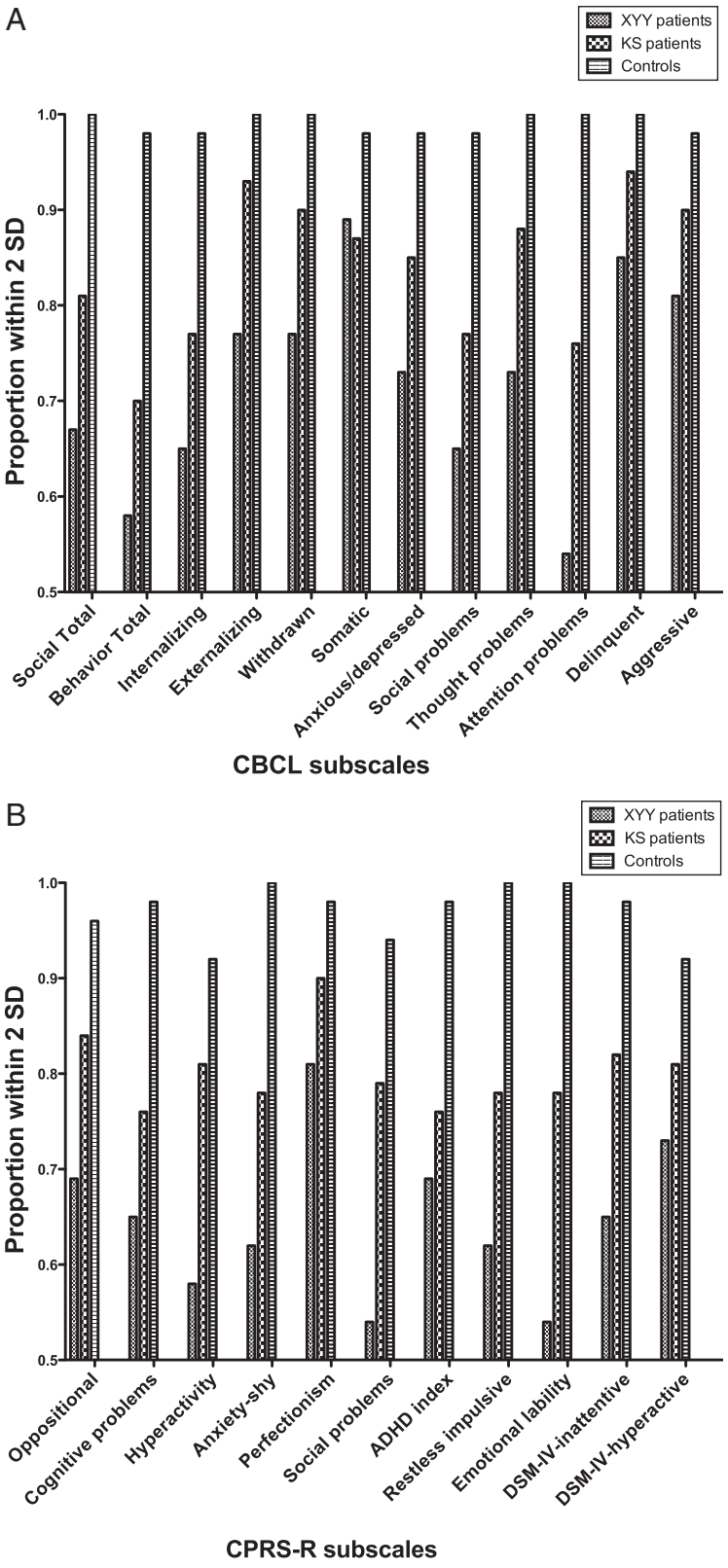

FIGURE 1

a, The proportion of participants with XYY, KS, and controls with *t* scores within ±2 SD for the CBCL subscales. B, The proportion of participants with XYY, KS, and controls with t scores within ±2 SD for the CPRS-R subscales.

TABLE 2 Analysis of Variance Parent Behavioral Questionnaires (Mean *t* Score ± SD)

	XXY	XYY	Controls	*P* value[a]
CBCL-Problem behaviors				
n	82	26	50	
Behavior summary scores (Lower is better)				
Behavior total	61.3 ± 12.0[b]	67.3 ± 10.0[c]	46.7 ± 10.0	.0001[a]
Internalizing total	59.3 ± 11.3[b]	62.7 ± 12.0[c]	46.0 ± 9.3	.0001[a]
Externalizing total	54.7 ± 12.7	61.3 ± 11.3[c,d]	46.0 ± 11.3	.0001[a]
Problem Behaviors				
Withdrawn	58.7 ± 9.30[b]	64.0 ± 11.3[c,d]	51.3 ± 3.3	.0001[a]
Somatic complaints	61.3 ± 8.70[b]	60.0 ± 9.30[c]	54.7 ± 6.0	.0001[a]
Anxious/depressed	59.7 ± 9.30[b]	62.7 ± 12.0[c]	52.0 ± 4.7	.0001[a]
Social problems	64.7 ± 10.7[b]	67.3 ± 11.3[c]	52.0 ± 4.7	.0001[a]
Thought problems	58.7 ± 8.70[b]	66.7 ± 10.7[c,d]	52.0 ± 4.0	.0001[a]
Attention problems	64.0 ± 11.3[b]	70.0 ± 10.0[c,d]	52.7 ± 4.7	.0001[a]
Delinquent behavior	57.3 ± 8.0[b]	60.0 ± 9.30[c]	52.0 ± 3.3	.0001[a]
Aggressive behavior	58.0 ± 10.0[b]	63.3 ± 10.7[c,d]	53.3 ± 5.3	.0001[a]
Sex problems	56.7 ± 10.0[b]	58.0 ± 12.0	52.0 ± 5.3	.01[a]
CBCL Social competence scales (Higher is better)				
Activities total	45.0 ± 7.30[b]	43.0 ± 8.0[c]	50.0 ± 6.0	.0001[a]
Social total	40.0 ± 10.0[b]	37.0 ± 10.7[c]	49.0 ± 6.0	.0001[a]
School total	33.0 ± 7.30[b]	31.0 ± 6.7[c]	50.0 ± 7.3	.0001[a]
CPRS (Lower is better)				
Oppositional	58.0 ± 12.0[b]	66.0 ± 12.0[c,d]	49.3 ± 8.7	.0001[a]
Cognitive problems/Inattention	62.0 ± 10.7[b]	66.7 ± 10.0[c]	47.3 ± 7.3	.0001[a]
Hyperactivity	57.3 ± 12.7	66.0 ± 12.7[c,d]	52.7 ± 10	.0001[a]
Anxiety-shy	59.3 ± 12.0[b]	62.7 ± 14.0[c]	49.3 ± 8.0	.0001[a]
Perfectionism	52.7 ± 10.7[b]	58.0 ± 12.7[c]	47.3 ± 8.0	.0001[a]
Social problems	60.0 ± 14.0[b]	69.3 ± 14.7[c,d]	48.7 ± 8.0	.0001[a]
Psychosomatic	60.7 ± 14.7[b]	58.0 ± 14.0[c]	49.3 ± 8.7	.003[a]
Global index: ADHD index	61.3 ± 11.3[b]	66.0 ± 9.3[c]	48.0 ± 8.0	.0001[a]
Global index: Restless/impulsive	59.3 ± 11.3[b]	66.0 ± 10.0[c,d]	50.0 ± 9.3	.0001[a]
Global index: Emotional lability	61.3 ± 12.0[b]	69.3 ± 12.7[c,d]	47.3 ± 8.7	.0001[a]
DSM-IV-Inattentive	60.7 ± 10.7[b]	66.0 ± 10.7[c,d]	48.0 ± 8.0	.0001[a]
DSM-IV Hyperactive-impulsive	58.7 ± 12.7[b]	66.0 ± 11.3[c,d]	52.0 ± 10.0	.0003[a]
DSM-IV total	60.0 ± 11.3[b]	66.7 ± 10.0[c]	50.0 ± 8.7	.0001[a]
SCQ (raw scores), (n)	7.6 ± 6.3 (34)	15.1 ± 9.9[c,d] (22)	2.9 ± 2.4 (31)	.0001[a]
% > cutoff = 15	4/34 (12%)	11/22 (50%)	0/31	.0001[a]

[a] ANOVA, comparison of 3 groups.
[b] $P < .05$, XXY versus controls, ANOVA (post hoc).
[c] $P < .05$, XYY versus controls, ANOVA (post hoc).
[d] $P < .05$, XYY versus XXY, ANOVA (post hoc).

2. CPRS-R:

In general, most of the boys in both the XYY and KS groups had scores within 2 SDs of the population mean (Fig 1B) for all domains of the CPRS-R. Comparison of the 3 groups revealed that both the XYY and KS groups had significantly higher mean *t* scores (more behavioral difficulties) compared with the control group for all CPRS-R scales ($P < .003$), except in the area of hyperactivity for the KS group, where there was no significant difference from the control group (Table 2). Compared with the KS group, the XYY group showed more behavioral difficulties in the domains of externalizing behaviors, withdrawal, thought problems, attention problems, and aggressive behaviors.

We next compared the proportion of each group with scores >90th percentile for the DSM-IV Inattentive scale, the DSM-IV Hyperactive/Impulsive scale, and the other CRPS-R subscales (Fig 2). The frequency of reaching or exceeding the 90th percentile differed significantly among the 3 groups ($P < .007$ for all CPRS subscales except Perfectionism, $P < .02$, Fisher's exact test). In the XYY group, 62% vs 41% of the KS group had *t* scores greater than the 90th percentile for DSM-IV Inattentive symptoms ($P < .006$), and 62% vs 30% of the KS group had *t* scores >90th percentile for DSM-IV Hyperactive/Impulsive symptoms. Of note, these results are similar to 12 (46%) of 26 XYY boys and 28 (34%) of 82 KS boys, who had been previously diagnosed with ADHD.

Prenatal diagnosis in utero was not a significant covariate for the boys with XYY. For the boys with KS, prenatal diagnosis was associated with better outcome in the Cognitive problems/Inattention subscale ($P < .04$).

3. SCQ:

Mean raw scores on the SCQ and the proportion of boys with scores exceeding the cutoff score of 15 were compared among the 3 groups to screen for possible autistic characteristics (Table 2). The 3 groups differed significantly ($P < .0001$); the KS and XYY groups had mean SCQ levels that were significantly higher than controls, and the XYY group was significantly higher than KS group ($P < .05$, Table 2). A total of 50% of the XYY group, 12% of the KS group, and none of the controls had SCQ scores above the cutoff of 15 ($P < .0001$, Fisher's exact test). A total of 8 (31%) of 26 boys with XYY versus 5 (6%) of 82 boys with KS had previously been diagnosed with ASD. Prenatal diagnosis was not a significant covariate for the XYY or KS groups.

Child Self-Report Anxiety and Depression Behavioral Questionnaire Results

There were no significant differences among the 3 groups for responses from self-report questionnaires for depression (Children's Depression Inventory) and anxiety (Revised Child's Manifest Anxiety Scale) (Table 3). Prenatal diagnosis was not a significant covariate for the XYY or KS groups.

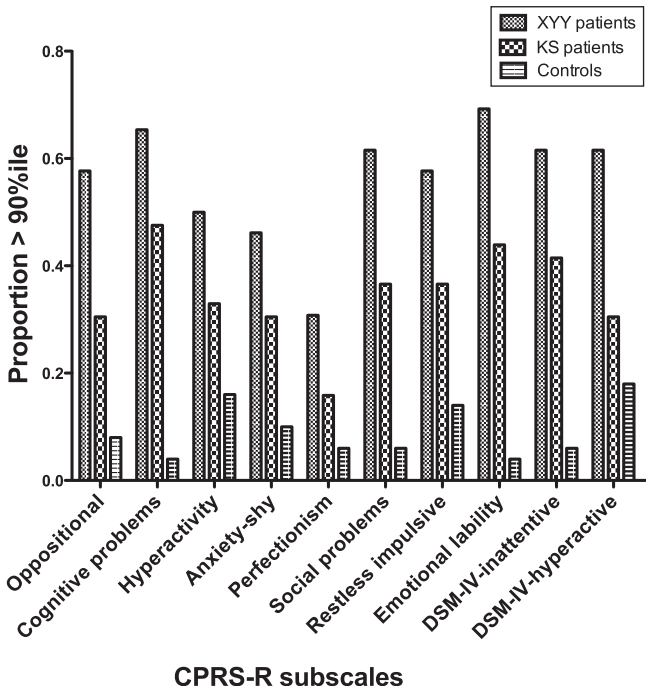

FIGURE 2
The proportion of participants with XYY, KS, and controls with *t* scores >90th percentile for the CPRS-R subscales.

DISCUSSION

The goal of this study was to compare and contrast behavioral and social phenotypes in boys with the sex chromosome disorders, 47,XYY and 47,XXY (KS) versus age-matched controls. The current study extends previous findings by providing data on a larger sample of boys with XYY or KS who were recruited from a wide geographic region on the basis of karyotype rather than psychological diagnoses. An advantage to comparing the XYY and KS groups in this study is that they have similar general cognitive abilities.[15]

Importantly, in previously published newborn screening studies and in the current study, there is significant variability within the groups, and many of the boys with XYY or KS did not show significant behavioral problems. Our results do indicate, however, that there is increased risk for significant behavioral problems in a subset of boys from the XYY and KS groups, in agreement with previous reports.[5,23,24,53] The behavioral phenotypes in the XYY and KS groups differed somewhat in that problem behaviors were more significant in the XYY versus the KS group. There did not seem to be increased anxiety or depressive symptoms in either group.

The behavioral phenotype previously described in XYY syndrome includes an increased risk of impulsivity,[5,23,24] poor adaptation to social situations, and behavioral problems related to externalizing behaviors.[16,17,24–30] Although our results support these increased risks, it is important to underscore that past research linking XYY to increased risk for criminality must be viewed with extreme caution, given their reliance on small sample sizes and selected rather than broader-based sampling approaches.

In our study, 62% of boys with XYY and 42% of boys with KS had significantly elevated symptoms of ADHD, based on the CPRS-R, compared with a 4% to 5% prevalence rate of ADHD in the general population.[54,55] Previous studies also report an increased risk for ADHD, including 11% of a cohort of 26 males with XYY,[11] and 63% in a group of 51 males with KS based on standardized DSM-IV interview.[56]

Half of the XYY group in the current study scored above the cutoff score on the SCQ for screening for ASD, versus 12% of the KS and none of the control group. These frequencies differ from the overall prevalence of ASD in the general population of ~1 of 125,[57] and are consistent with previous reports,[11,32–34] suggesting there may be an increased risk for ASD features, particularly in

TABLE 3 Child Anxiety and Depression Questionnaires (Mean *t* Score ± SD)

	XXY	XYY	Controls	*P* Value[a]
CDI (Lower is better)				
n	67	16	38	
Total	47.3 ± 8.7	48.7 ± 10.0	44.7 ± 7.3	.20
Negative mood	47.3 ± 9.3	48.0 ± 10.0	46.0 ± 7.3	.60
Interpersonal problem	49.3 ± 9.3	50.0 ± 10.0	47.3 ± 6.7	.38
Ineffectiveness	47.3 ± 9.3	50.0 ± 10.7	44.7 ± 6.7	.12
Anhedonia	50.0 ± 10.7	50.7 ± 10.0	46.7 ± 8.0	.17
Negative self esteem	46.0 ± 6.7	45.3 ± 8.7	45.3 ± 7.3	.87
RCMAS (Lower is better)				
n	67	17	38	
Total anxiety	50.7 ± 12.7	48.7 ± 8.7	46.7 ± 10.0	.21
Physiologic	49.3 ± 12.7	49.3 ± 9.3	44.0 ± 10.7	.09
Worry/Oversensitivity	50.0 ± 11.3	47.3 ± 9.3	46.7 ± 8.7	.29
Social concerns	51.3 ± 10.0	47.3 ± 8.7	46.0 ± 8.7	.25
Lie scale	48.7 ± 12.0	53.3 ± 9.3	51.3 ± 10.7	.74

CDI, Children's Depression Inventory; RCMAS, Revised Child's Manifest Anxiety Scale.
[a] ANOVA, comparison of 3 groups.

the XYY group. The behavioral phenotype of both XYY and KS includes features that overlap considerably with ASD, such as language disorders, other social deficits, and anxiety/withdrawal symptoms. Additional diagnostic studies are needed to determine whether male subjects with XYY or KS indeed meet criteria for ASD by using standardized autism assessments.

Interestingly, the XYY but not the KS group tended to have increased head circumference relative to the control group, in agreement with most,[11,17,33] but not all[58] previous studies. Brain imaging studies have demonstrated relatively reduced brain volumes in boys with KS.[59] In contrast, increased head circumference and increased brain volumes have also been reported in a subset of children with autism.[60–62] Future imaging studies will define the underlying brain structure related to these findings in XYY.

Potential factors related to the observed behavioral differences in the XYY and KS groups are their age at diagnosis and the reason for diagnosis. Ascertainment from clinic samples referred for developmental and behavioral issues[63] could affect the description of the XYY phenotype. Previous studies have supported better neurodevelopmental outcomes in prenatally versus postnatally diagnosed KS cohorts,[25] likely reflecting differences in SES, genetic, and environmental factors in the 2 groups and less bias toward behavioral/developmental findings in boys diagnosed prenatally. In agreement, we also noted relatively better outcomes in prenatally versus postnatally diagnosed boys with KS. We did not find a significant impact of prenatal diagnosis in the XYY group, most likely reflecting the smaller sample size and fewer prenatally diagnosed subjects in this group. Most (59%) of our KS cohort but only 23% of the boys with XYY were diagnosed prenatally. Most (77%) of the boys with XYY were diagnosed postnatally on the basis of developmental or behavioral issues, which would create a sampling bias for more severe behavioral features in our sample. Also, in contrast to KS, the diagnosis of XYY is often delayed.[11,30,64] Milder behavioral findings would perhaps also have been found in a larger, prenatally diagnosed XYY cohort; however, subsets of boys with XYY ascertained without bias from newborn screening studies also have behavior findings,[18,40,65] suggesting that the association with the karyotype is genuine.

We previously noted considerable overlap in the XYY and KS groups for cognitive function.[15] The similarity of findings in these 2 genetic disorders may be related to overlapping gene dosage abnormalities in the pseudoautosomal region (PAR1), a 2.6-Mb interval at the tips of Xp and Yp, where genes are equally expressed.[66,67] Similarly, tall stature in both of these populations is thought to be attributable to increased expression from 3 instead of 2 copies of the height-determining SHOX gene.[68]

The distinctions in behavioral phenotypes of KS and XYY may be related to hormonal and/or genetic factors that differ between the 2 groups. The clearest hormonal difference is normal testosterone in XYY versus testosterone deficiency in KS; behavioral effects of testosterone are well known.[69] Genetic factors that differ in XYY versus KS are related to the extra X chromosome in KS versus the extra Y chromosome in XYY. Because a substantial fraction of genes on the X escape X-inactivation to some degree,[70] these genes would be overexpressed in the KS group only. The parental origin of the extra chromosome may differentially affect KS and XYY because in KS, the supernumerary X chromosome may be maternal or paternal, whereas in males with XYY, the extra Y chromosome is always paternal in origin. Notably, no parent of origin difference in the KS phenotype has been conclusively demonstrated.[71–74]

The extra Y chromosome in XYY remains active, and expression of all Y-linked genes is increased in the XYY group only. Previously, the Y chromosome was thought to have a relatively small number of sex-determining and testicular function genes, but is now known to contain additional genes.[75,76] Given the increased proportion of boys with XYY versus KS with elevated screening SCQ scores, we hypothesize that the ASD-like behavioral features in XYY are based on an abnormal dosage of 1 or more of these Y-specific genes. Y chromosome candidate genes with potential neural impact include *PCDH11Y* (protocadherin 11Y),[77] *TBL1Y* (transducin β-like 1, Y-linked),[78,79] and *NLGN4Y* (neuroligin 4 Y).[78,79] Mutations of the closely related, X-linked gene *NLGN4*× (neuroligin 4 X) have been firmly implicated in autism/ASD and mental retardation (reviewed in ref 80).[81,82]

CONCLUSIONS

These behavioral phenotype results provide support for clinical care recommendations and counseling in XYY and KS. Given the increased risk for developmental and behavioral findings, boys diagnosed with either XYY or KS should receive a comprehensive psychoeducational evaluation and be screened for learning disabilities, ADHD, and ASDs. Educational and behavioral interventions can help address these issues in school and home settings and should be provided to the subset identified as having learning disabilities or psychological/behavioral difficulties to reduce the risk of long-term sequelae. Attention deficits are too common in boys to justify widespread screening for sex chromosomal abnormalities on the basis of this behavioral indication; however, genetic evaluation

should be considered when ADHD is coupled with significant language delays and physical findings, such as tall stature or signs of atypical testicular development. Helpful resources and contacts through advocacy groups include KS&A (Knowledge, Support and Action, www.genetic.org) and UNIQUE: Rare Chromosomal Disorder Support Group (www.rarechromo.org). Next steps will need to focus on identifying underlying genetic, neurobiological, and environmental factors contributing to the variability and severity of behavioral and psychological symptoms in XYY and KS and on the development of evidence-based treatments.

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A GARDEN OF EDEN: *Every year we plant a garden. We don't plant anything particularly exotic, just vegetables we like to eat. While we have fruit trees, the birds eat all our cherries before we can, the apples always have fungal infections, and the plums and apricots never fruit. Although each year I am a bit disappointed with my harvest, my frustrations are probably nothing like those who plant biblical gardens. As reported in* The Wall Street Journal *(February 11, 2012), many individual gardeners, synagogues, and churches in different areas across the U.S. including Vermont have attempted to recreate gardens from herbs, fruit trees and flowers described in the Bible. Many, if not most, have learned that successful cultivation of plants native to the Middle East can be remarkably challenging when grown in the U.S. In this day of international commerce and internet access, purchasing the seeds or seedlings is easy. Specialized gardening groups with expertise in Middle Eastern plants offer advice and support. Books, in a range of prices, are available for the burgeoning biblical gardener. The hard part, however, is getting the plants to grow, survive the pests and weather of a very different environment, and finally fruit. Many biblical gardeners have story after story of their failings. Occasionally, biblical gardens, such as the wonderful garden of the Cathedral of St. John the Divine in New York City, thrive. However, the annual maintenance budget for the Cathedral of St. John the Divine biblical garden is $20,000 and hordes of expert gardeners volunteer their time. For many gardeners, faith, hard work, and persistence are not enough to overcome the challenge of growing non-native species. Still, congregations persist in their efforts as a biblical garden can attract new members and help build stronger community bonds. As for me, I know that despite my best efforts I will never successfully cultivate a pomegranate or olive tree in northern Vermont. However, I will continue to battle the pests and weather for a crop of zucchini and tomatoes and strive to arrange a visit to the biblical gardens in New York.*

Noted by WVR, MD

Behavioral and Social Phenotypes in Boys With 47,XYY Syndrome or 47,XXY Klinefelter Syndrome

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